TENT COOPERATION TRE. Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 March 2001 (14.03.01)	
International application No. PCT/GB00/02567	**Applicant's or agent's file reference** PHM.70558/WO
International filing date (day/month/year) 03 July 2000 (03.07.00)	**Priority date** (day/month/year) 06 July 1999 (06.07.99)
Applicant SHAW, John, Edward, Andrew et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 January 2001 (23.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

GB0002567

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau

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11 January 2001 (11.01.2001)

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(10) International Publication Number
WO 01/02834 A1

(51) International Patent Classification[7]: G01N 13/00, 35/00

(21) International Application Number: PCT/GB00/02567

(22) International Filing Date: 3 July 2000 (03.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915686.1 6 July 1999 (06.07.1999) GB

(71) Applicant *(for all designated States except US)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SHAW, John, Edward, Andrew [GB/GB]; 45 Colne Avenue, West Drayton, Middlesex UB8 2LQ (GB). TURNER, Christopher, Matthew [GB/GB]; 56 Waterside, Uxbridge, Middlesex UB8 2LQ (GB). LAW, Brian [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: BROWN, Andrew, Stephen; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

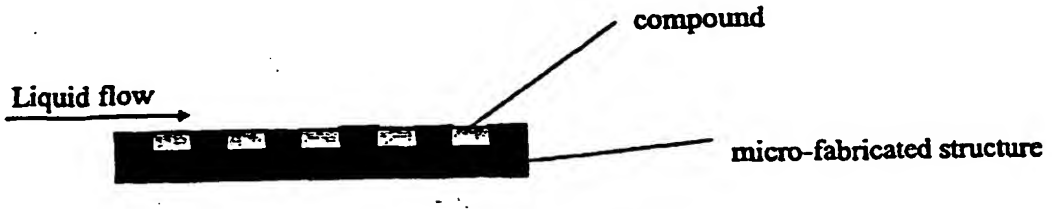
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MICRO-FABRICATED SOLUBILITY MEASURING SYSTEM AND A METHOD FOR DETERMINING THE SOLUBILITY OF A SAMPLE



(57) Abstract: The invention relates to a micro-fabricated device for the measurement of the solubility or the rate of dissolution of a sample. Specifically the invention relates to an automated device for the determination of these parameters in large numbers of samples.

WO 01/02834 A1

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM.70558/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02567	03/07/2000	06/07/1999
International Patent Classification (IPC) or national classification and IPC		
G01N13/00		
Applicant		
ASTRAZENECA UK LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/01/2001	08.10.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Thomte, M

409

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02567

I. **Basis of the report**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16 as originally filed

Claims, No.:

1-4 as originally filed

Drawings, sheets:

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-4
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-4
Industrial applicability (IA)	Yes:	Claims 1-4
	No:	Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

ad Section V

1. Reference is made to the following documents:
   D1: WO-A-9845701
   D2: Chemistry And Industry. Chemistry And Industry Review,gb,chemical Society. Letchworth (05-10-1998), (19), 792-793
   D3: US-A-5858195
   D4: Journal Of Micromechanics & Microengineering,us,new York, Ny (01-12-1994), 4(4), 257-265
   D5: WO-A-0022428

2. Document D1 (see e.g. Figure 3 with the text belonging to it) reveals a measuring system for *inter alia* measuring the solubility of a sample. The system comprises a small volume region for introducing a predetermined amount of liquid to the region and a detector (24) which is able to directly or indirectly determine whether solid sample is removed from the region by the liquid.
   The subject-matter of claims 1 and 2 differ from what is known from D1 merely in that they refers to a *micro-fabricated* solubility measuring system - which, seemingly, is not used in document D1.

3. However, the measure of down-scaling or shrink chemical and biological measurement systems down to a micro-level provides for a number of advantages which is clear to the skilled person in the art - see e.g. document D2.
   Thus, the skilled person having a system such as that of D1 and being faced with the problem of wanting to minimize his apparatus - e.g. in order to improve its portability, or, in order to enhance its on-site usability - would, when having regard to the teaching of document D2, not hesitate to consider the possibility of micro-fabricating his system. In doing so one would inevitably arrive at the subject-matter of claims 1 and 2 which therefore do not fulfil the requirements of Article 33(3) PCT as to inventive step.

4. The methods of Claims 3 and 4 do also not fulfil the requirements of Article 33(3) PCT for reasons similar to those set out above, *mutatis mutandis*.

5. It is not at present apparent which part of the application could serve as a basis for a new claim which would fulfil the requirements as to inventive step as set out in Article 33(3) PCT.
If the application is pursued in the national or regional phase a new independent claim should be filed containing the particular subject-matter which the applicant regards being patentable. The applicant should - when filing such a regional or national application - also indicate in a letter accompanying the application, the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.

ad Section VIII

6. Although claims 3 and 4 have been drafted as separate independent claims, they appear to relate effectively to the same method and to differ from each other only with regard to the definition of the subject-matter for which protection is sought or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the two different independent claims could make it difficult, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the exact extent of the protection. Hence, claims 3 and 4 do not meet the requirements of Article 6 PCT.

ad Section VII

7. In pursuing the application in the national or regional phase, then the following matters should also be dealt with:

(I) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 - D4 is not mentioned in the description, nor are these documents identified therein.

(ii) Any new independent claim to be filed should be drafted in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be

appropriate, with those features known in combination from the prior art (document D1) being placed in the preamble (Rule 6.3(b)(I) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

(iii) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT).

PATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PHM.70558/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02567	03/07/2000	06/07/1999
Applicant		
ASTRAZENECA UK LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

MICRO-FABRICATED SOLUBILITY MEASURING SYSTEM AND A METHOD FOR DETERMINING THE SOLUBILITY OF A SAMPLE

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTE TIONAL SEARCH REPORT

[redacted]ational Application No
PCT/GB 00/02567

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N13/00 G01N35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 45701 A (LI JIANMIN ;ANDERSON BRADLEY D (US)) 15 October 1998 (1998-10-15) page 5, line 1 -page 6, line 13 page 7, line 26 -page 11, line 6 figure 3 ---	1-4
Y	COWEN S: "SMALL IS BEAUTIFUL" CHEMISTRY AND INDUSTRY. CHEMISTRY AND INDUSTRY REVIEW,GB,CHEMICAL SOCIETY. LETCHWORTH, no. 19, 5 October 1998 (1998-10-05), pages 792-793, XP000779581 ISSN: 0009-3068 the whole document --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2000	27/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thomte, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 858 195 A (RAMSEY J MICHAEL) 12 January 1999 (1999-01-12) column 1, line 21 -column 2, line 35 column 6, line 31 -column 6, line 44 abstract	1-4
A	MANZ A ET AL: "ELECTROOSMOTIC PUMPING AND ELECTROPHORETIC SEPARATIONS FOR MINIATURIZED CHEMICAL ANALYSIS SYSTEMS" JOURNAL OF MICROMECHANICS & MICROENGINEERING,US,NEW YORK, NY, vol. 4, no. 4, 1 December 1994 (1994-12-01), pages 257-265, XP000601273 ISSN: 0960-1317 cited in the application abstract paragraph '01.3!	1-4
A	DE 19 66 830 A (BOEHRINGER SOHN INGELHEIM) 11 July 1974 (1974-07-11) the whole document	1-4
A	DE 195 37 179 C (LOEFFLER HANS PETER) 10 April 1997 (1997-04-10) the whole document	1-4
A	US 4 578 244 A (COSGROVE JR ROBERT J ET AL) 25 March 1986 (1986-03-25) abstract	1-4
A	US 5 837 446 A (LAUKS IMANTS R ET AL) 17 November 1998 (1998-11-17) column 1, line 19 - line 63	1-4
P,X	WO 00 22428 A (MILLER BRYAN JAMES ALAN ;SHAW JOHN EDWARD ANDREW (GB); LAW BRIAN () 20 April 2000 (2000-04-20) the whole document	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02567

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9845701 A	15-10-1998	US 6004822 A	21-12-1999
		AU 6880398 A	30-10-1998
US 5858195 A	12-01-1999	US 6001229 A	14-12-1999
		US 6010607 A	04-01-2000
		US 6010608 A	04-01-2000
		US 6033546 A	07-03-2000
		AU 701348 B	28-01-1999
		AU 3150895 A	04-03-1996
		CA 2196429 A	15-02-1996
		CN 1168720 A,B	24-12-1997
		EP 0775306 A	28-05-1997
		JP 10507516 T	21-07-1998
		WO 9604547 A	15-02-1996
DE 1966830 A	11-07-1974	NONE	
DE 19537179 C	10-04-1997	WO 9714035 A	17-04-1997
		EP 0853763 A	22-07-1998
US 4578244 A	25-03-1986	AU 1608983 A	21-11-1983
		CA 1210252 A	26-08-1986
		EP 0106892 A	02-05-1984
		WO 8303901 A	10-11-1983
US 5837446 A	17-11-1998	US 5466575 A	14-11-1995
		US 5200051 A	06-04-1993
		US 5554339 A	10-09-1996
		US 5837454 A	17-11-1998
		CA 2002848 A	14-05-1990
		CA 2221178 A	14-05-1990
		EP 0442969 A	28-08-1991
		JP 2000065791 A	03-03-2000
		JP 4503249 T	11-06-1992
		US 5063081 A	05-11-1991
		US 5212050 A	18-05-1993
		WO 9005910 A	31-05-1990
		KR 175917 B	15-05-1999
		SG 45431 A	16-01-1998
WO 0022428 A	20-04-2000	AU 6114899 A	01-05-2000

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM.70558/WO

Box No. I TITLE OF INVENTION

DEVICE

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1Y 6LN
GB

☐ This person is also inventor.

Telephone No.
(01625) 516485

Facsimile No.
(01625) 583358

Teleprinter No.
669095/669388

State *(that is, country)* of nationality:
GB

State *(that is, country)* of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
SHAW, John Edward Andrew
45 Colne Avenue
West Drayton
Middlesex
UB8 2LQ
GB

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
GB

State *(that is, country)* of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
BROWN, Andrew Stephen et al
ASTRAZENECA
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4GR
GB

Telephone No.
(01625) 514620

Facsimile No.
(01625) 583358

Teleprinter No.
669095/669388

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

See Notes to the request form

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TURNER, Christopher Matthew
56 Waterside
Uxbridge
Middlesex
UB8 2LQ
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LAW, Brian
Alderley Park
Macclesfield
Cheshire
SK10 4TG
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V. DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** GHGhana, GM Gambia, KE Kenya, LS Lesotho, MWMalawi, SDSudan, SL Sierra Leone, SZSwaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** AMArmenia, AZAzerbaijan, BY Belarus, KG Kyrgyzstan, KZKazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** ATAustria, BEBelgium, CH and LISwitzerland and Liechtenstein, CY Cyprus, DEGermany, DK Denmark, ESSpain, FIFinland, FRFrance, GB United Kingdom, GRGreece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BFBurkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, MLMali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent*(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
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☒ **IL** Israel .....
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☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
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☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
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☒ **US** United States of America .....
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☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ **DZ** Algeria .....
☒ **AG** Antigua .....

Precautionary Designation Statement In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 06 JULY 1999 (06/07/99)	9915686.1	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA /

Request to use results of earlier search; reference to that earlier search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets

request	: 4
description (excluding sequence listing part)	: 16
claims	: 1
abstract	: 1
drawings	: 7
sequence listing part of description	:
Total number of sheets	29

This international application is accompanied bythe item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

BROWN, Andrew Stephen et al

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

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Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/031040

Applicant's or agent's file reference SP16998JCI	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR00/02030	International filing date (*day/month/year*) 13 July 2000 (13.07.00)	Priority date (*day/month/year*) 16 July 1999 (16.07.99)
International Patent Classification (IPC) or national classification and IPC B63B 21/66		
Applicant GECO AS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 22 January 2001 (22.01.01)	Date of completion of this report 20 November 2001 (20.11.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR00/02030

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☒ the international application as originally filed.

☒ the description, pages 1-6, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-10, filed with the letter of 06 June 2001 (06.06.2001).
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/1, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____.
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

2. Citations and explanations

The subject matter of the claims as drafted does not involve an inventive step (PCT Article 33(3)).

Reference is made to the following documents:

D1: US 3 760 761
D2: US 4 549 499

1. Claim 1

The subject matter of **Claim 1 does not involve an inventive step** (PCT Article 33(3)).

Document D1 concerns a towed line kite for carrying out a variety of measures at sea. D1 therefore belongs to the same technical field as the subject matter of the present application.

The kite of D1 describes (see the whole document) the following features of Claim 1:
a towed line kite, including a streamlined horizontal portion (2), an upper portion (3, 4, 5, 6, 7, 1) rising towards the top of the horizontal portion (2), with the horizontal portion (2) completely submerged and the upper

portion (3, 4, 5, 6, 7, 1) partially submerged (part 6, 7) when the kite supports an element (see abstract, lines 1-3) of the line.

The device of document D1 differs from the subject matter of Claim 1 in that in D1, it is not explicitly specified that a flotation apparatus is concerned. In D1, it is not specified whether the kite remains on the surface of the water when it is not driven by a watercraft. Consequently, the kite of D1 cannot be considered to be a flotation apparatus.

The problem that the present invention is intended to solve can therefore be considered to be that of providing a device as described in D1 that does not sink in the water when the device is no longer driven by a watercraft.

It is well known from the prior art that in order to increase the buoyancy of a device, it is sufficient to construct it with a larger volume. Moreover, the use of a flotation apparatus in the field of towed line devices to carry out a variety of measures at sea such that said devices float is well known from the prior art (see D2).

In consideration of the above points, combining the set of features disclosed in Claim 1 is an ordinary technical step for a person skilled in the art. The subject matter of Claim 1 does not therefore involve an inventive step.

2. Claims 3-7, 10

D1 contains the set of added features contained in Claims 3-7 and 10. Consequently, the subject matter of said claims does not involve an inventive step (PCT Article 33(3)).

3. Claims 2, 8 and 9

The subject matter of Claim 2 as drafted is not considered to involve an inventive step (PCT Article 33(3)).
Indeed, in D1, the upper portion (3, 4, 5, 6, 7, 1) rises in part (see element 4) at the rear of the horizontal portion and therefore the present wording of Claim 2 cannot be considered to involve an inventive step.

The subject matter of Claims 8 and 9 does not involve an inventive step (PCT Article 33(3)).
Indeed, the fin keel housing in a slide of an element as well as the presence of horizontal fin keels on an element (in the case of D1, they are present on the vertical element 4) are well known in the prior art.

MICRO-FABRICATED SOLUBILITY MEASURING SYSTEM AND A METHOD FOR DETERMINING THE SOLUBILITY OF A SAMPLE

The invention relates to a micro-fabricated device for the measurement of the solubility or the rate of dissolution of a sample. Specifically the invention relates to an automated device for the determination of these parameters on large numbers of samples.

The determination of the solubility of a sample or its rate of dissolution are important in various areas of the drug discovery process since many processes of interest to the research scientist are dependant on the solubility or rate of dissolution of the sample. Examples where this information is of value would include interpreting data of a sample in; an *in vitro* assay, oral absorption test, formulation studies, and *in vivo* bioavailability studies.

Currently the pace of change in techniques and tools for discovery of biologically active molecules is increasing with the ability of combinatorial chemistry and multi-parallel synthesis (MPS) to rapidly provide large numbers of diverse samples to enter into the drug discovery process. In addition the mapping and sequencing of the genomes of many plants, animals and parasites, and the human genome, is already providing a growing number of new targets which may be used in biological tests. In the future it is to be expected that the number of biological targets is to grow even further. It is estimated that in the last 100 years of research only 400 human drug targets have been discovered whilst the human genome project will have sequenced at least 100,000 genes, many of which will code for important biological targets for drug therapy.

However, synthetic techniques such as MPS and combinatorial chemistry provide relatively small sample sizes, for example in the microgram range. The limited sample sizes currently produced are not large enough to supply more than a few tests within the drug discovery process before the supply is exhausted. Therefore, resynthesis is required in order to restock the chemical library.

In order to accelerate the rate of discovery of biologically active molecules, there is currently considerable interest in the measurement of physicochemical properties very early in the discovery process so that these factors may be used to influence future decisions on which

molecules to synthesis as samples for future testing. However, as described above, samples of potential interest may only be available in relatively small amounts i.e. <1 mg. There is therefore a strong need for methods of measuring solubility and rate of dissolution that can be applied to large numbers of samples without requiring proportionately more resources, and which are capable of dealing with small sample sizes. Conventional methods often employ complex separation steps which are time-consuming. Although these can be automated, the serial nature of the analysis, i.e. one sample at a time, still effectively limits the throughput. Automation may also lead to increased compound demands which is counter to the thrust of modern synthetic methods such as combinatorial chemistry and MPS and related technologies which, typically, do not produce large quantities of material. Therefore, for the large number of samples which are being prepared for testing, the traditional methods of measuring physicochemical properties are now prohibitively expensive and time consuming and can be performed on no more than a small percentage of the samples being prepared.

Currently the techniques for the determination of solubility involve stirring the sample in an appropriate solvent until a saturated solution has been achieved, removing the excess compound, typically by filtration or centrifugation, and then analysing the resulting solution using some physical method, for example HPLC, MS or UV detection, one example of which is direct UV analysis. This method is tedious, labour intensive, requires a sample size of at least 1mg, and the requirement for a physical separation can result in the production of erroneous data. One disadvantage of this technique is that fine solid particles may be suspended in the saturated solution. To avoid this disadvantage separation techniques need to be thorough, for instance centrifugation typically is required at least twice for each sample, which adds further to the expense and time needed to achieve a measurement. To determine the rate of dissolution of a sample involves the need to make a number of measurements over a period of time. This increases test times, and also proportionately the amount of sample required.

Therefore, there is a need to find simple, sensitive, high throughput approaches to the measurement of the solubility or rate of dissolution of a sample, especially in the pharmaceutical and agrochemical industry. Such a system should use small sample sizes, be quick (less than 3 hours) and be amenable to operation by a machine with minimal operator

input. In particular, miniaturised approaches operating on the picolitre / nanolitre / microlitre scale are particularly desirable, because of the large cost savings, potential for high throughput, and use of small sample sizes. Currently we are aware of no such techniques available which fulfil all the above requirements.

Micro-fabricated devices have been used to develop laboratory techniques on the micro scale which require minimal operator involvement using very small amounts of sample.

Micro-fabrication techniques are generally known in the art using tools developed by the semiconductor industry to miniaturise electronics, it is possible to fabricate intricate fluid systems with channel sizes as small as a micron. These devices can be mass-produced inexpensively and are expected to soon be in widespread use, for example, in simple analytical tests. See, e.g., Ramsey, J.M. et al. (1995), "Micro-fabricated chemical measurement Systems," Nature Medicine 1:1093-1096; and Harrison, D.J. et al (1993), "Micro-machining a miniaturized capillary electrophoresis-based chemical analysis system on a chip," Science 261:895-897.

Miniaturisation of laboratory techniques is not a simple matter of reducing their size. At small scales different effects become important, rendering some processes inefficient and others useless. It is difficult to replicate smaller versions of some devices because of material or process limitations. For these reasons it is necessary to develop new methods for performing common laboratory tasks on the micro-scale.

Devices made by micro-machining planar substrates have been made and used for chemical separation, analysis, and sensing. See, e.g., Manz, A. et al. (1994), "Electroosmotic pumping and electrophoretic separations for miniaturized chemical analysis system," J. Micromech. Microeng. 4:257-265.

We have devised a micro-fabricated device which can be used to determine solubility and rate of dissolution with minimal operator involvement using very small amounts of sample.

We disclose as the first feature of the invention a micro-fabricated solubility measuring system comprising a microfabricated device having a region in the device for receiving solid sample and a liquid inlet for introducing a predetermined amount of a liquid to the region together with a detector which determines directly or indirectly if solid sample is removed from the region by the liquid.

We disclose as the first feature of the invention a micro-fabricated solubility measuring system comprising a micro-fabricated device having a region in the device for receiving solid sample and a liquid inlet for introducing a predetermined amount of a liquid to the region together with a detector which determines directly or indirectly amount of solid sample removed from the region by the liquid.

In this disclosure, the term "sample" includes any material, single compound or mixture, which may be put into solid form, whether biological or chemical, preferably the sample is an organic synthetic compound, ideally of MW <1000.

In this disclosure, the term "region" means an area within the micro-fabricated device, which is able to accept and retain an amount of solid sample and allow that solid sample to come into contact with liquid in the device. The region may be formed as a surface on which solid material can be deposited and adhere as a continuous or discontinuous layer. Such a surface may already be part of the surface of the micro-fabricated device or may be applied as a coating. Preferably the surface incorporates one or more physical structures which define the region, such as indents, which aid retention of defined quantities of solid sample. The volume defined by the region may be in the range of sizes which may be created in micro-fabricated devices as described above, such as by etching or building up structures or by moulded replication of structures. Typical region volumes include from 1 nl to 1 µl. Typical dimensions across regions may be in the range of sizes which may be created in micro-fabricated devices, typical ranges are from 10-1000µm, preferably 10-100µm.

Indents may be in the form of extended slots or grooves where the long dimension may exceed 1000µm. It will be appreciated that any number of indents may be arranged on the same

device, such as to form a pattern, such as a line or grid pattern. An indent may be formed by a depression in the surface of the microfabrocate device or within a raised structure on the microfabricated device. The indents may be sufficiently large to retain all the sample or large enough to retain at least part of the sample the remaining part being above the indent.

The process of deposition of sample into the region may involve compaction such that the solid cannot be physically washed away but must be removed by a process of dissolution, see Figure 1. Alternatively the sample may be deposited by other processes of application such as a spray or, alternatively, the sample may be deposited from a solution by creating local environments in the region, such as a hydrophobic surface, which forces the compound out of solution, or by evaporation of the liquid and subsequent deposition of the sample. The process of deposition may be assisted by use of coatings to the surface of the region to attract and bind the sample. The solid sample is transferred to the region so that the amount and thickness of sample is controlled and measurable. Control of sample amount and thickness may be facilitated by features such as indents in the surface of the sample receiving region or by other means such as by applying sample to the microfabricated surface through a screen of known thickness, by controlling weight or volume of sample, and by deposition to the microfabricated surface of more sample than required and then removing excess by machining or etching means, and by combinations of such procedures. Sample deposition methods may include pressing solid sample onto a receiving surface, or deposition of mixtures or solutions of the sample in volatile carrier fluid. Samples may not be pure. Additionally the sample may contain solid material which may be insoluble in the solvent used to determine the solubility measurement and added to the sample to aid deposition and/or for formation of a controlled thickness of sample. Such solid materials which may be added may include fibres or ballotini.

The term "detector" includes devices, probes, sensors, indicators or such like which are able to determine the presence or absence of solid sample remaining in the region, either with or without the liquid present, or which are at least able to detect the presence or absence of sample, preferably the detector is able to measure, directly or indirectly the amount of solid sample remaining or removed from the region. The detector may operate alternatively by measuring sample present in the liquid. Examples of such detector methods include interferometry where the intensity of interference patterns of reflected light on the surface of

the device show the depth of sample in indents, surface acoustic wave sensors, elipsometry, use of radiation sources and sensors measuring attenuation though the solid sample layer, image analysis, spectrophotometry, chromatography or electrophoresis. Physical methods of detecting or measuring the depth of the sample in the region may be employed such as the use of a stylus.

The detector of the system may be separate to the micro-fabricated aspects of the system ("off-device") or in a preferred alternative option may also be an integrated micro-fabricated feature of a micro-fabricated solubility device ("on-device"). A variety of different detection methods are described below as preferred features:

1. The thickness of the solid sample is defined by means of a micro-engineered feature such as an indent which allows integral calibration for detection methods applied to a range of solid samples whose physical properties such as refractive index and spectral absorbencies are not known a priori. This is particularly valuable for elipsometry.

2. Most solid samples of interest are insulators or at least poor conductors of electricity. Dissolution of such solid samples from an electrode surface into an ionically conducting liquid may be monitored by electrical impedance measurements. Indents formed so that the base only of indents is electrically conducting allows those conductive bases to be used as electrodes. Coverage of the conductive indent bases may be monitored using electrical impedance between electrode and solution, with a substantial decrease in impedance signalling the dissolution of material covering the electrode.

3. Direct detection or measurement of the dissolved sample in solution can be difficult, such as by the use of UV or visible radiation detection methods, if the sample is only weakly absorbing or fluorescent. Alternative indirect technique may be used which employ direct measurements of indicator material. In one indicator based method a thin layer of a selected indicator material deposited on the solid receiving region and then covered with the solid sample. Preferably the indicator material is

deposited as a thin film over the bases of any indent which is then filled with solid sample. Exposure of the indicator material or release of the indicator material into solution is delayed until sample dissolution is near completion, and its appearance on the surface or in solution acts as an end point signal. Indicator materials may be detected on or off device by the use of, for example, UV detection of fluorescent compounds. Low mobility and relatively low solubility, in the solvent used, indicator compounds are preferred so that the indicator does not permeate through the sample nor promote release of the sample from the surface. In a second indicator bed method , the indicator is mixed with the sample so that the dissolution of the sample releases indicator into the solution, dissolved or suspended, and the quantity of such released indicator is used as a measure of the sample dissolution. The indicator for this method should not interact with the substance being measured and may be a fine insoluble powder.

4. As an alternative to producing indent type structures in the solid sample receiving region which are filled with sample and then progressively revealed as dissolution proceeds an optically monitorable feature may be produced by a series of features made from solid sample on a plane surface of the microfabricated device. These features may form diffraction structures. Where the diffraction structures are formed by indents the process of sample dissolution allows development of the diffraction pattern, while for diffraction structures formed from the sample on a plane surface the process of dissolution is accompanied by a decrease in the size of the features and reduction in the intensity of any diffraction effects. Such raised features formed from the solid samples may be formed by deposition through masks or grids but do require that the sample adheres well to the substrate surface. The use of indented structures provides more tolerance of variation in physical properties and sample substrate adhesion.

Additionally the device may contain an outlet for removal of the liquid where the liquid is desired to be removed in order for the particular detector used to make the requisite measurement.

We disclose as a further feature of the invention a method for determining the solubility of a sample in a micro-fabricated device the method comprising:

(1) introducing a predetermined amount of liquid to a solid sample containing region within the micro-fabricated device;

(2) measuring the amount of solid sample removed from the region by the liquid;

(3) determining the solubility of the sample by reference to the measurement of solid sample removed from the region and the amount of liquid used.

Due to the smaller quantities of liquid and sample which may be used diffusional distances within the liquid can be dramatically lowered allowing for equilibrium to be reached efficiently without the need for convective or advective mixing. However movement of liquid may be employed to enhance or control dissolution rates.

Different samples will reach the point of equilibrium at different rates, this is known as the rate of dissolution. The rate of dissolution of a sample may be affected by many different factors such as the morphology or surface area of the sample, chemical kinetic factors at the solid/ solution interface, permeation of pores within the solid by solvent, and transport of dissolved material in the solvent by convective, advective, or diffusive processes. Within microstructures it is possible to limit convective or advective and in particular turbulent fluid transport so that diffusion may be the dominant mode of transport of dissolved material. Where diffusive transfer is the limiting factor the dissolution rate is related to the length of the path through which the dissolved solute molecules diffuse and the geometry of the fluid body. Diffusive transfer rates will generally be inversely related to the square of the path length.

Typically diffusion coefficients (D) of samples of the size range of interest (MW of a few hundred) will be $\sim 10^{-6}$ cm^2s^{-1} and have diffusive transfer times across a path length (L) which may be derived from expressions of the type $Dt/L^2 = 0.01$ to 1 second, where $Dt/L^2 = 0.01$ approximates to a diffusion front reaching a distance L from source plane, and $Dt/L^2 = 1$ corresponds to near completion of the diffusive process (concentration gradient across ***L*** being nearly eliminated). Approximate times for reaching diffusive equilibration ($Dt/L^2 = 1$) at different path lengths (L), in which the solid material must travel, based on $D = 10^{-6}$ cm^2s^{-1} are:

L = 10 μm	t= 1 sec
L = 100 μm	t= 100 sec
L = 1 mm	t= 2.8 hours
L =1 cm	t= 280 hours

About 50% of the diffusive transfer will occur in about a tenth of the above times. Based upon a static liquid for relatively rapid equilibration by diffusion alone the distance L across the liquid from solid surface should not be greater than 100 μm. This has an impact on the liquid volume which may be used in static liquid device of the invention, i.e. preferably a liquid volume up to 10nl, preferably up to 5nl.

The consequent limitation on liquid volume can however be readily removed if the liquid is mixed by convective/advective processes within the device and this is a further feature of the invention. Most simply the fluid is stirred *in situ*, e.g. by small magnet stirrer, such as beads, or the fluid may be recirculated over the solid. Alternatively the liquid may be removed to a mixer chamber and then reintroduced to the compound. This may avoid problem with mechanical abrasion on the solid solute surface generating suspended matter, and may be more compatible with *in situ* observation/monitoring of the dissolving solid surface.

Typical amounts of sample which may be used in this device range from 1 ng to 1 mg, the minimum figure corresponds to the region being and indent corresponding to a 10 micron side cube. Typical amounts of liquid used in this device range from 1 nl to 1 ml, the minimum liquid volume corresponds to a 100 μm side cube. A chamber within the device for presenting liquid to the solid sample need not be in the form of a cube but for rapid diffusive transfer no portion of fluid within the chamber should be maintained at a distance from the solid sample much greater than 100μm. It may be useful to present a small solid filled indent to a very large volume of stirred liquid to determine a maximum dissolution rate in the absence of any tendency to saturate.

It will be appreciated that a true measurement of the solubility of the sample is only possible once sufficient time has elapsed for the sample to be fully dissolved and equilibrium is reached.

It will be appreciated that the amount of liquid used will limit the maximal measurement of solubility that may be determined, for example if 0.01mg of solid sample is fully dissolved in 0.01ml of liquid then the maximum determined measurement of solubility of the sample is - at least 1mg/ml- the exact measurement could be close to this figure or higher. However, in certain fields it is more useful to determine which samples are poorly soluble in a certain solvent, or that a sample has at least a certain value of solubility in a solvent. Therefore, such limitations are not necessarily critical and the amount of liquid used may be selected such that if all the sample is dissolved in the liquid then the solubility of the samples is acceptable or if any sample remains then the sample is not sufficiently soluble. In such systems it is not necessary that the detector measures the amount of solid sample removed from the region by the liquid. The detector need only determine the presence or absence of compound in the region. Where the amount of solid sample deposited in the region and the amount of liquid is known then the absence of any solid sample at the region after exposure to the liquid indicates a minimum solubility that the sample possesses. The parameters of sample deposited and liquid used may be set such that the minimal solubility measured is at a cut of point to indicate whether the sample passes or fails the test.

It is possible that the rate of dissolution of a sample can be measured in the same system or device as described above by measuring the amount of sample removed from the region by the liquid at various time points before equilibrium is reached.

As a further feature of the invention we disclose a method for determining the rate of dissolution of a sample in a micro-fabricated device the method comprising:

(1) introducing a liquid to a solid sample containing region within the micro-fabricated device;

(2) at time points after introduction of the liquid measuring the amount of solid sample removed from the region;

(3) determining the rate of dissolution by reference to the measurement of solid sample removal from the region and the amount of liquid used over time.

Measurement of rate of dissolution may be carried out where the liquid, preferably of predetermined volume, is presented to the solid sample and remains static while measurements are performed. Alternatively dissolution rates may be carried out by measurement with the liquid volume stirred or recirculated, as described above, or where fresh liquid is fed through the chamber containing the solid sample receiving region.

Additional steps which may be performed in the above methods include extracting the liquid prior to taking the measurement of solid sample removed from the region and/or an initial step of introducing the solid sample into the region of the micro-fabricated device.

It should be understood that the arrangement, type and dimensions of the device and the components therein will vary according to the use or application.

In this disclosure, the term "micro-fabricated" includes devices including structures capable of being fabricated with lengths in one or more dimensions of less than 1 mm, and especially fabricated on or into planar solid substrates such as silicon wafers using methods readily available to those practising the art of silicon micro-fabrication. Such micro-fabricated devices may have feature of sizes and geometries producible by such means such as photolithography, isotropic and anisotropic etching by wet or dry methods, thick and thin film deposition methods including printing, screen printing, spin and dip coating, evaporation, sputtering, chemical vapour deposition, LIGA, thermoplastic micro-pattern transfer, resin based micro-casting, micro-moulding in capillaries (MIMIC), laser assisted chemical etching (LACE), and reactive ion etching (RIE), or other techniques known within the art of micro-fabrication. Planar substrates such as silicon wafers may accommodate single devices or a plurality of the devices of this invention in the same or a plurality of configurations. Wafers are available with standard sizes which include wafers with diameters of 3" (7.5cm), 4"(10cm), 6"(15cm), and 8"(20cm), but the structures may be formed on substrates of other dimensions. Application of the principles presented herein using new and emerging micro-fabrication methods is within the scope and intent of the invention.

In this disclosure, the term "liquid" means any liquid for which the solubility of the sample is desired to be determined within, for example aqueous, non-aqueous, protic, aprotic, buffered or non-buffered, or mixtures of any thereof. The liquid may interact with the solid sample simply to achieve physical dissolution alone or may effect some chemical reaction including ionisation, ligand addition, solvation or hydrolysis. Liquid is introduced to the region such that the liquid and solid sample are brought into contact. Ideally the liquid is delivered as a predetermined volume of liquid. The liquid may be delivered such that it remains static over the solid sample for a period of time prior to or after the measurement is made by the detector. Alternatively the liquid may be streamed across the solid sample containing region and the measurement taken during or after streaming has been completed. In a further alternative the liquid is streamed over the sample several times by continuous recirculation or by an oscillating motion of the liquid. In a further alternative version the liquid is removed from the solid sample, mixed, and then reintroduced to the solid sample. Motion of the liquid may be achieved by the use of physical forces, such as pressure, inertial forces, capillary forces, or the application or variation of electric or magnetic fields. Non liquid fluids such as super critical fluids and gases and vapours may be substituted for liquids in the above description with the process of dissolution into a liquid being equated generally to the transfer of solid as molecular species into the fluid phase. For gases or vapours the process of solid transfer into the gas phase which may be characterised may include evaporation, sublimation, or reaction such as oxidation generating gaseous or volatile products.

In many of the structures and methods described within a fixed quantity of solvent fluid is presented to the solid substance. This may be delivered as slug of fluid between two regions of a second fluid immiscible with the solvent and in which the solid is not able to dissolve .

This other fluid might preferably be a gas,such as air or nitrogen, or argon, The slug of solvent fluid could be driven into or through the region containing the solid substance or repeated exposure of the solid substance to the solvent can be achieved by oscillating the fluid slug by pumping of the second fluid. The solvent fluid may be moved to a solution analysis region where it can be measured/monitored by an analytical means such as UV absorption or mass spectrometry. A slug of solvent may be driven repeatedly between substance contact and the analytical region to allow dissolution rate to be monitored towards saturation and determination f the solubility.

As described above the option to recirculate or mix the liquid allows for a larger volume of liquid to be used without unduly extending the time needed to allow diffusional equilibrium. Therefore, in a preferred aspect, liquid of up to 1 ml or above may be used, preferably up to 0.5ml, and ideally up to 100µl.

By high throughput we mean that the invention can achieve a throughput substantially higher than conventional means often 10 to 100 fold increases. In order to achieve the higher throughputs, the method optionally involves parallel processes, i.e. multiple indents are used in parallel. One sample may be tested with several different liquids or several samples may be tested with one or several liquids.

The invention also allows for the simple measurement of the rate of dissolution by placing several identical samples in parallel regions and for each sample exposing it to the liquid for different periods of time. Alternatively the above mentioned process may also simultaneously measure solubility by allowing one or more samples to equilibrate with the liquid. Alternatively the rate of dissolution is measured by taking measurements of the solid sample remaining in the indent at various time points after application of the liquid, necessitating a detector which can operate with the liquid present on the sample, and optionally a final measurement of solubility once equilibrium has been reached.

In particular we describe as a feature of the invention an on device detection system where the disappearance of the solid is determined using optical techniques, such as interferometry, see Fig 2. The light focused on the sample produces an interference pattern on a suitable focusing device by virtue of the scale and the physical arrangement of features of the grid or mesh and

the wavelength of light. As the compound dissolves the intensity of the interference pattern will change. The rate of change will be related to the rate of dissolution of the compound.

The invention is illustrated below by the following non-limiting examples.

Examples

Optical Detector

Using an arrangement as shown in Figure 2 a diffraction pattern is produced, where the horizontal surfaces of the micro-fabricated device are reflective and the compound is less reflective than the surface of the micro-fabricated device. As the compound dissolves lower reflective horizontal surfaces of the micro-fabricated device are exposed. This will not affect the position of the diffraction pattern but will intensify the lower order diffraction bands. Whilst we do not wish to be bound by theory the intensity of the bands is governed by the formula

$$I(\theta) = \frac{I(O)}{N^2} (\mathrm{Sin}\beta/\beta)^2 (\mathrm{SinN}\alpha/\mathrm{Sin}\alpha)^2$$

where I (θ) is the central peak intensity, N is the number of grating lines and where

$$\alpha = \frac{ka}{2} \quad \text{and} \quad \beta = \frac{kb}{2}$$

where k is the order number, a is the pitch of the grating and b is the width of the reflective horizontal surfaces of the micro-fabricated device.

Therefore, as compound dissolves 'a' will remain constant and 'b' will increase. At the point that all compound dissolves the surface will be completely reflective and there will be no diffraction pattern. To avoid complicating interference effects the difference in path length for reflections from each layer of reflective surface will preferably be multiples of the wavelength of light in the medium in which measurements are carried out. Where measurements are carried out without removal of the solvent the medium will be the solvent

used. For light incident at an angle θ normal to the reflective surfaces, the height difference between reflective surfaces should preferably be multiples of ¼ of the wavelength of light and cosine θ. To enable this restriction to be more easily accommodate the light source may include or encompass a range of wavelengths and the detection system provide wavelength selectivity, for example by the use of filters.

Alternatively, some wells or areas of wells of the device shown in Figures 1 and 2 may be left unfilled with compound while others contain compound so that the unfilled areas provide a reference. Where the liquid has been allowed to reach an equilibrium composition, the inclusion of such reference wells without solid sample content allows compensation for effects of refractive index and refractive index change.

Figure 3 shows the output expected from a device of Figure 2.

Alternative grating based optical methods may be used to measure the dissolution of solid compound from a surface. Using structures of the type represented in Figure 4 allows the periodicity of a grating to be altered as solid compound dissolves. In the example shown in Figure 4 the dissolution of sample within the indents so that the solid sample surface initially at position 1 is changed to position 2 exposing a reflective surface in the centre of a well or trench will double the number of lines per unit length of the grating. This change in grating period enables detection by means of a change in diffraction angles or spectral shift. Similar arrangements where other changes in grating feature spacing are achieved may be achieved by different positioning of reflective surfaces in the wells.

An alternative arrangement indicated in Figure 5 employs the progressive exposure of a group of adjacent steps to generate an expanding grating or reflective surface which can be monitored optically.

Electrochemical Detector

Forming a series of wall structures overlying a conductive electrode structure allows sample to be retained on the electrode surface contained in indents. Exposure of the electrode by dissolution of the sample is monitored by monitoring a cell impedance as indicated in Figure 6

Mass Detector

Alternatively we describe a device where disappearance of the compound is detected by piezo sensors such as quartz crystal devices and which may include Surface Acoustic Wave sensors, which are particularly suited to operation on a miniaturised scale. Such sensors provides an output related to the mass of material adherent to the device surface. A plane mass sensor with sample feature formed on the structure is illustrated in Figure 7.

Claims

1. A micro-fabricated solubility measuring system comprising a microfabricated device having a region in the device for receiving solid sample and a liquid inlet for introducing a predetermined amount of a liquid to the region together with a detector which determines directly or indirectly if solid sample is removed from the region by the liquid.

2. A micro-fabricated solubility measuring system as claimed in claim 1 wherein the detector determines directly or indirectly the amount of solid sample removed from the region by the liquid.

3. A method for determining the solubility of a sample in a micro-fabricated device the method comprising:
(1) introducing a predetermined amount of liquid to a solid sample containing region within the micro-fabricated device;
(2) measuring the amount of solid sample removed from the region by the liquid;
(3) determining the solubility of the sample by reference to the measurement of solid sample removed from the region and the amount of liquid used.

4. A method for determining the rate of dissolution of a sample in a micro-fabricated device the method comprising:
(1) introducing a liquid to a solid sample containing region within the micro-fabricated device;
(2) at time points after introduction of the liquid measuring the amount of solid sample removed from the region;
(3) determining the rate of dissolution by reference to the measurement of solid sample removal from the region and the amount of liquid used over time.

Fig.1

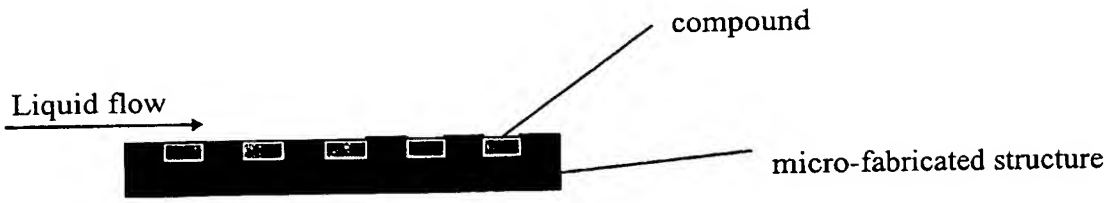
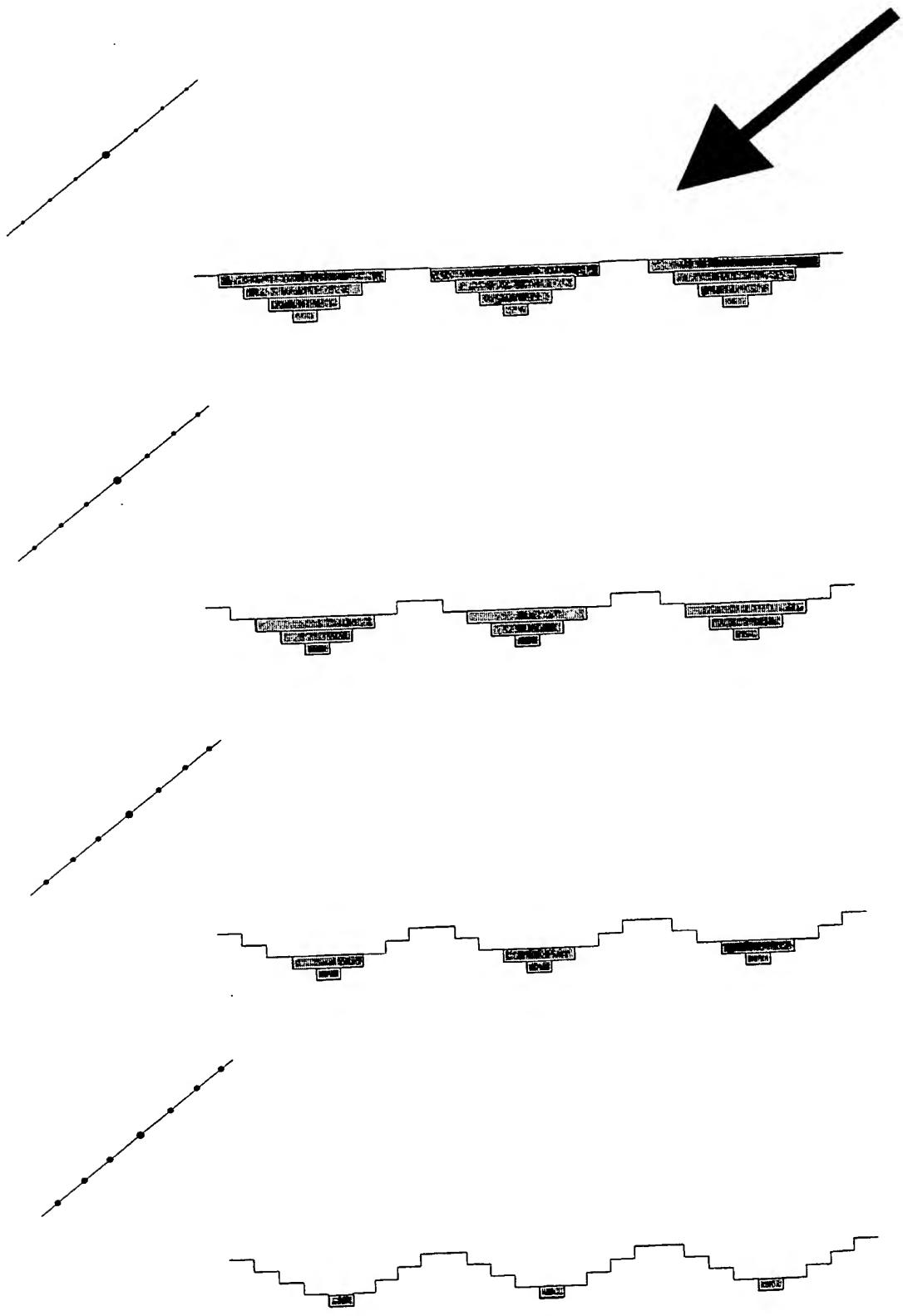
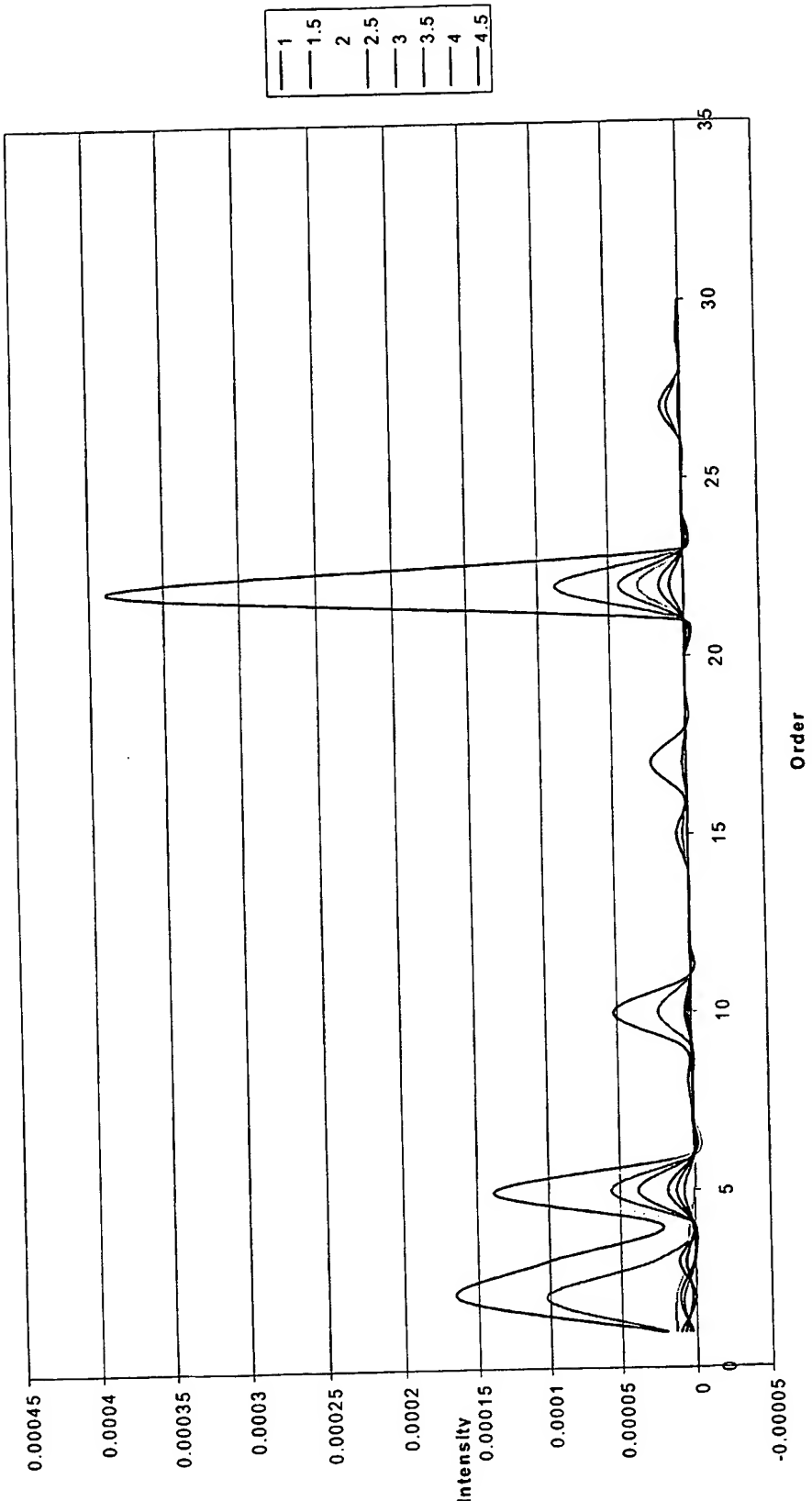


Fig.2

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0.00015
0.0001
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15
20
25
30
35
Order

Fig.3

70558

Fig.4

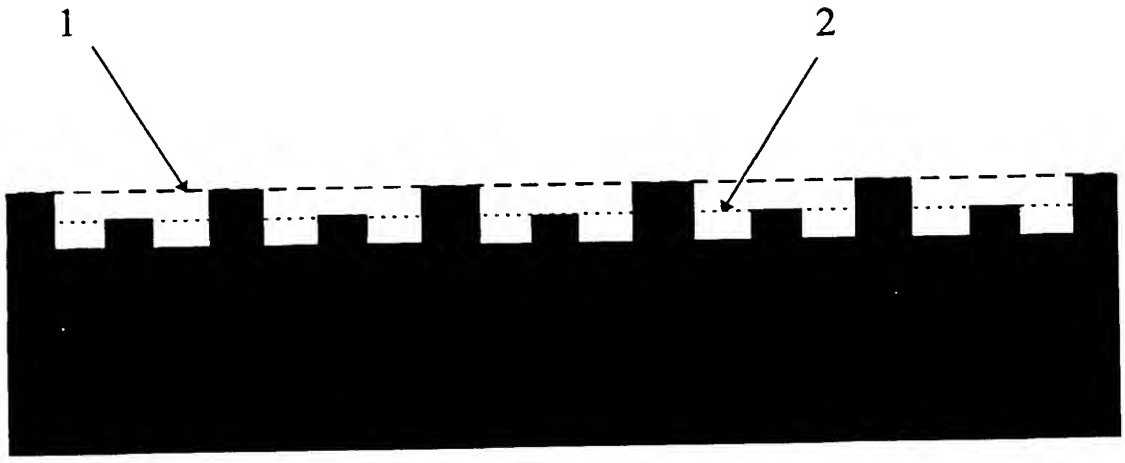


Fig.5

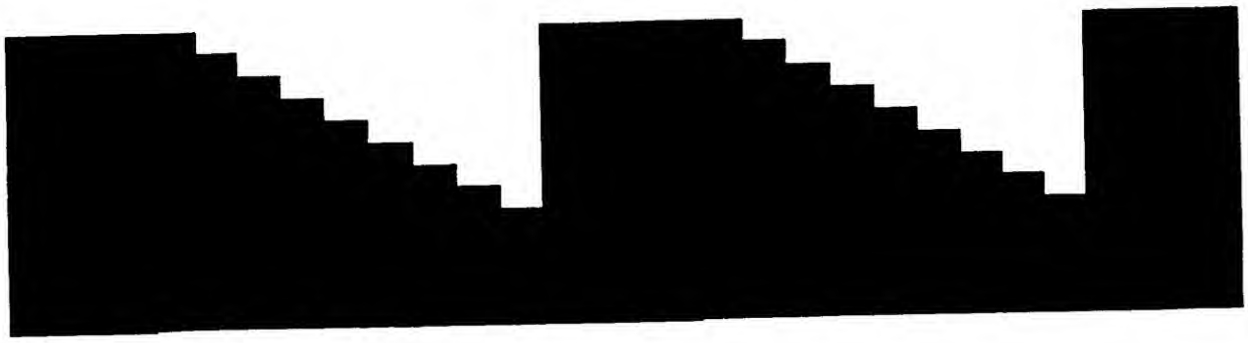


Fig.6

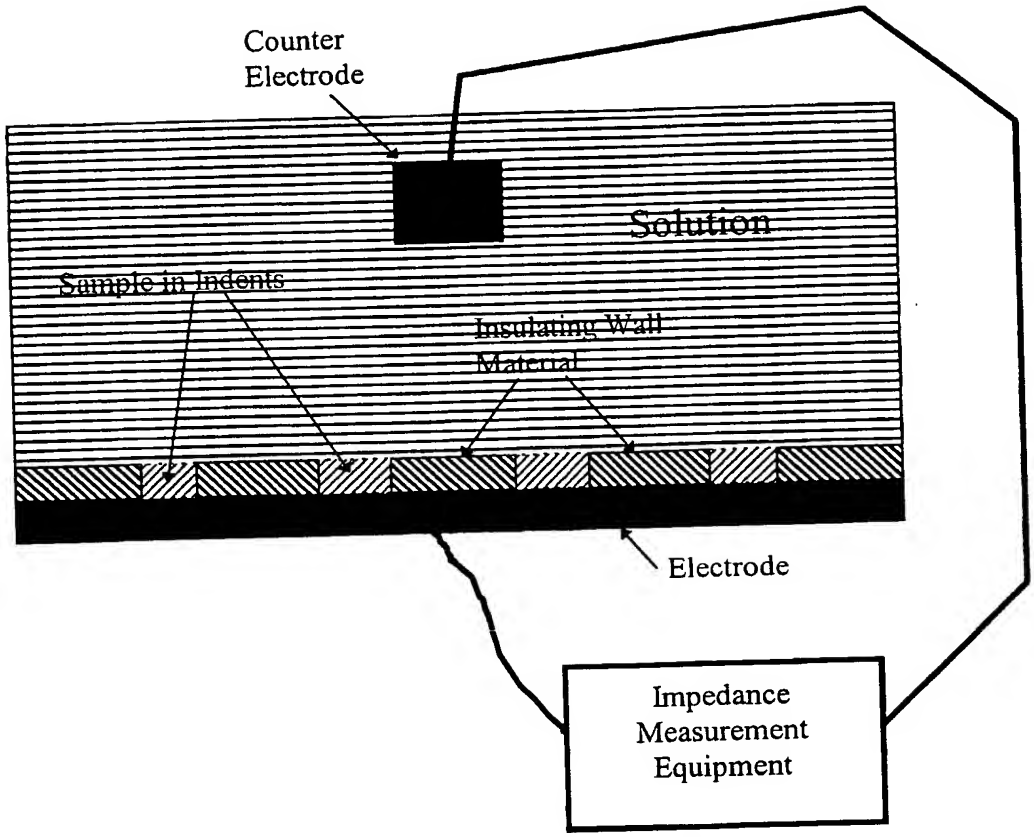
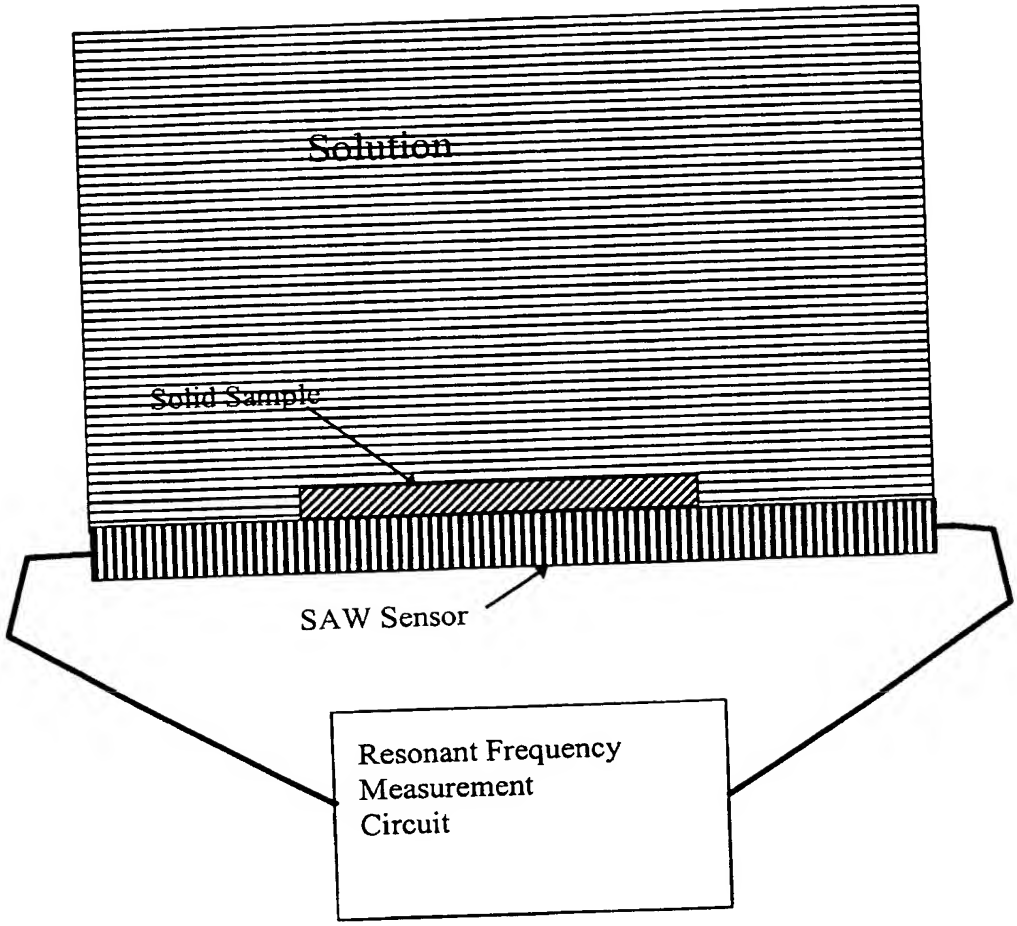

Counter
Electrode
Solution
Sample in Indents
Insulating Wall
Material
Electrode
Impedance
Measurement
Equipment

Fig.7


Solution
Solid Sample
SAW Sensor
Resonant Frequency
Measurement
Circuit

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/GB 00/02567

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N13/00 G01N35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	COWEN S: "SMALL IS BEAUTIFUL" CHEMISTRY AND INDUSTRY. CHEMISTRY AND INDUSTRY REVIEW,GB,CHEMICAL SOCIETY. LETCHWORTH, no. 19, 5 October 1998 (1998-10-05), pages 792-793, XP000779581 ISSN: 0009-3068 the whole document --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2000	27/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Thomte, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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